The Impact of Advertising on Statin Drug Adherence and Attaining LDL Cholesterol Goals

W DAVID BRADFORD [1, 2]
ANDREW N. KLEIT [3, 4]

[1] *Center for Health Economic and Policy Studies, Medical University of South Carolina*
[2] *Department of Health Administration and Policy , Medical University of South Carolina*
[3] *Department of Meteorology, Pennsylvania State University*
[4] *Center for Health Care Policy, Pennsylvania State University*

Address for Correspondence: W David Bradford, Ph.D., Center for Health Economic and Policy Studies, Department of Health Administration and Policy, Medical University of South Carolina, 151 Rutledge Avenue, Building B, Charleston, SC 29425; Tel: 843-792-2117; E-mail: bradfowd@musc.edu

This paper was funded by grants from the Agency for Healthcare Research and Quality (1 R01 HS011326-01A2) and from the National Heart Lung and Blood Institute (1 R01 HL077841-01).We thank Ruth Jenkins, M.S. for assistance in supporting the extract of clinical data from the PPRNet system, and Olena Verbenko, M.S. and Michael Kunz, M.S. for assistance in constructing the analysis data sets.

1. INTRODUCTION

Other than New Zealand, the United States is the only industrialized country to permit relatively unrestricted television and radio advertisement for pharmaceutical products that can be obtained only by prescription. This practice of advertising directly to consumers through print and broadcast media has been accelerating since the mid-1990s. The practice was further reinforced in August of 1997 when the Food and Drug Administration (FDA) clarified and relaxed apparent restrictions on what pharmaceutical companies could say in short television and radio advertisements promoting prescriptions medications. Despite the ubiquity of Direct to Consumer (DTC) advertising today, it remains controversial and the FDA has begun hearings to re-evaluate its relative liberal regulatory stance.

While the issues surrounding DTC have increased in importance,, there are relatively few empirical studies examining the impact of DTC at the patient level. This paper will examine the impact of DTC on the health of patients with hypercholesterolemia (generally defined as elevated Low Density Lipoproteins (LDL) which is the main culprit in developing of vascular plaques and other cardiovascular disease) using a unique clinical dataset. In particular, we will test the joint hypotheses that DTC for a class of cholesterol reducing drugs known as statins (e.g., Lipitor, Pravachol, and Zocor) affects both the adherence of patients to their prescribed pharmacologic therapies, and the LDL levels that patients achieve as a result of treatment.

In Section II of this we paper examine the policy issues around DTC. We also discuss their application to statin prescriptions, which are used to reduce cholesterol levels. Section III presents our data and hypotheses. Section IV contains our results, while Section V has concluding comments.

2. BACKGROUND

2.1. Literature on DTC

The practice of advertising directly to consumers through print and broadcast media has been accelerating since the mid-1990s. The practice was further reinforced in August of 1997 when the Food and Drug Administration (FDA) clarified and relaxed restrictions on what pharmaceutical companies could say in short television and radio advertisements promoting prescriptions medications. Despite the ubiquity of Direct to Consumer (DTC) advertising today, it remains controversial and the FDA continues to hold hearings on the subject.

DTC advertising for pharmaceuticals is highly controversial. There are a variety of economic arguments both support and opposing DTC. The beginnings of the current policy debate on DTC may date to Masson and Rubin [1]. This article makes several points about the merits of consumer advertising for pharmaceuticals. First, advertising can help consumers to realize that they suffer from an undiagnosed medical condition. For example, thanks to an ad campaign by Pfizer, many people who had been experiencing persistent thirst may have learned that thirst is a symptom of diabetes. Drug advertising also provides information about new treatments to consumers who suffer from diagnosed medical conditions. These effects are probably the two most-cited benefits of DTC by supporters of drug advertising. (See also Rubin [2] and Keith [3].)

On the other side of the argument, one of the recurring themes among critics of DTC is concern that the practice could intrude on the agency relationship between physicians and patients (e.g., J. Weissman et al. [4]). Fundamentally, the issue has merit—if patients hire physicians with superior medical knowledge to make decisions regarding diagnoses and treatment, then it is unclear what new information can be added by DTC. Theoretical problems with DTC along these lines are discussed in Brekke and Kuhn [5]. The work of these authors suggests that DTC can raise prices to patients if DTC is a complement of detailing, or may cause over-consumption if pharmaceuticals have low insurance copayments. Given all this, the medical

community is divided about the efficacy of DTC. (A measure of the deep ambivalence toward DTC in the medical community can be found in Holton (2005).)

With the theoretical effects of DTC uncertain, it is natural to turn to the empirical works on the subject. Several studies from the immediate post-1997 period examined aggregated data on pharmaceutical DTC marketing and sales. Calfee, Winston and Stempski [6] examined whether the August 1997 policy change at FDA increased the demand for the statin class of drugs using national aggregate drug sales by class, but was unable to find any significant short run direct effects. These authors suggest that the best way to examine this question may be to look at data on the patient level. There are, however, only a limited number of studies of DTC that use actual patient data. A study by Zachary et. al. [7] used the National Ambulatory Medical Care Survey (NAMCS), along with national frequencies of advertising for a number of drug classes to examine frequencies of monthly prescribing for 1992 – 1997. While that study found some significant relationships, the measured impacts of DTC are not consistent. Iizuka and Jin [8] used also utilized the NAMCS and found that DTC tended to prompt relatively large increases in physician visits and modest changes to the nature of the physician/patient interaction (thought longer visits), bud did not prompt significant changes to actual physician prescribing. Wosinska [9], using a four-year panel of data from Blue-Shield of California, found that while patient adherence to prescribed statin therapy did rise, the effect was small in magnitude and not sufficient in and of itself to yield a positive return on investment for the pharmaceutical manufacturers. Like much of the other literature, she also found class effects in DTC spending.

Donohue et al. [10] explored an administrative database that included actual prescriptions filled at the patient level (though it did not have patient clinical information) and focused on the use of anti-depressants. They found that DTC for antidepressants led to higher rates of diagnosis of depression and prescribing, but much smaller increases in appropriate adherence to therapy. Two aspects of their models will be important in this analysis. First, (along with much of the other literature) they estimated models where DTC was defined at a class-level (DTC for all brands within an

individual drug class was aggregated). Second, they expressed the DTC effect by quartiles of DTC intensity, and created a set of indicator variables for DTC exposure, rather than including DTC as a simple linear effect.

Two other recent studies are of particular note for this paper. These studies used the same clinical database that we utilize and examined the impact to DTC on the use of Cox-2 inhibitors (Celebrex and Vioxx). Bradford et. al. [11] examined the rate of prescribing of Celebrex and Vioxx to osteoarthritis patients at the physician practice level. This paper found that increases in DTC lead to a greater flow of patients with osteoarthritis into the practice to seek care, consistent with the patient selection hypothesis of Rubin and Masson. Bradford et. al [12] examined the delay between diagnosis with osteoarthritis and the adoption of daily use of a Cox-2 inhibitor. Using patient comorbidities, the authors were able to identify patients who had indications in favor of Cox-2 inhibitor use, and patients who had contraindications for Cox-2 inhibitor use. Interestingly, the results of this work strongly indicated that DTC was effective at encouraging adoption among patients with favorable indications and discouraging adoption among patients with contraindications.

2.2. Clinical Issues

Coronary Heart Disease (CHD) is the leading cause of mortality in the United States – causing nearly 460,000 deaths in the U.S. in 1998 [13]. Over 12 million people in the U.S. have some history of CHD. High cholesterol (hyperlipidemia) has been identified as a primary risk factor in CHD. Further, this condition is amenable to treatment using pharmaceutical therapies – primarily one of the statins (atorvastatin (Lipitor), simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor), fluvastatin (Lescol), etc.). Statins have been demonstrated to be highly effective at not only reducing levels of cholesterol in the blood to clinically acceptable baselines but also at reducing mortality from CHD. Statin benefits have been measured in the range of a 34 percent reduction in relative risk for coronary events to a 42 percent relative risk reduction in coronary mortality [14]. For hyperlipidemia , we will focus on prescribing

patterns for the most popular statins. In our data, the most frequently used brands are Lipitor, Pravachol, and Zocor.

The FDA has approved the use of statins for the treatment of hyperlipidemia and coronary artery disease. Guidelines for the treatment of hyperlipidemia are regularly published. The latest guideline released was the Third Report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults published in 2001 (known as ATP III) [15]. This report emphasizes the importance of non-pharmacologic intervention for the prevention and treatment of hyperlipidemia. This method of treatment, entitled therapeutic lifestyle changes, includes reduced intakes of saturated fats and cholesterol, increased physical activity and weight control. The use of statins is then based upon lipid measurements and a patient's risk factors. For patients with 0 – 1 risk factors, statins are not indicated unless LDL levels are greater than 160 milligrams per deciliter (mg/DL) of blood volume. For patients with 2 or more risk factors and a 10 – 20 percent 10 year risk for heart disease, statins should be started in patients with LDL levels greater than 130mg/dL. For patients with known coronary artery disease or its equivalent, statins should be used for patients with LDL levels greater than 100 mg/DL.

These standards guide clinical practice in the use of statin therapy for control of hyperlipidemia. In the analysis that follows we will create clinical indicators that mimic these guidelines. Using a detailed clinical database we will evaluate the degree to which DTC affects how likely patients are to adhere to prescribed lipid-lowering therapy and move below the treatment thresholds defined in the ATP III.

3. DATA AND HYPOTHESES

3.1. Conceptual Issues

The nature of treatment of dyslipidemias in the U.S. must drive the specific empirical implementation of the theoretical framework discussed above. Clinical management of elevated blood cholesterol levels has evolved over the years as evidence

has been generated from randomized drug trials, long panel studies of defined populations, and evaluation of retrospective datasets. The National Cholesterol Education Program periodically conducts expert panel assessments of the evidence and makes recommendations to physicians regarding treatment processes and blood cholesterol targets. As mentioned above, the most recent such guidelines, referred to as ATP III guidelines, were published by the National Heart, Lung and Blood Institute in 2001. These guidelines set bands for what would be considered optimal, borderline, high, and very high levels of blood cholesterol – which is best measured as the level of LDL mg/DL. These guidelines represent thresholds, or targets, such that therapies will be adjusted until the target threshold is met.

Thus, while one might be tempted to model the impact of statin treatment (and the derived effect of DTC advertising on the outcome) in terms of changes in measured LDL mg/DL, the resulting estimator would be biased. To see why, consider the treatment process using statins for high cholesterol. One characteristic of these drugs is that the effect, in terms of LDL reductions, will largely depend upon the dose of the drug taken (and so be limited by the patient's tolerance for any side effects). Generally, clinicians will start at the lowest dose that they believe can achieve the goals, and re-test the patient. If the goal is not met on re-test, then the strength of the prescription will be raised until the target LDL level is met. Now, consider two hypothetical patients. Assume the first patient comes in with two risk factors for coronary heart disease, but is not yet diagnosed with the condition, and has an LDL lab value of 150 mg/DL. The ATP III guidelines call for a target LDL level of 130 mg/DL – so the patient begins statin therapy, and achieves goal after a 20 point drop in the LDL level. A second patient comes in with an LDL lab value of 200 mg/DL. Again, if this patient initiates treatment then the dosage will be titrated until she also achieves goal (130 mg/DL of blood). Clinically, then, both patients have achieved the recommended treatment goal. However, one has done so after achieving a 20 mg/DL drop in LDL blood levels, while the other has done so after achieving a 70 mg/DL drop in the LDL measurement. Both the 20 mg/DL drop and the 70 mg/DL drop in LDL values achieve – in one meaningful sense – the desired clinical outcome.

How then should one model this process? In essence, there are two separate questions: "What effect does DTC have on reducing LDL blood levels, irrespective of whether clinical targets are met?" and "What effect does DTC have on helping patients achieve LDL clinical goals?" While both are important (since any significant reduction in LDL levels is thought to have clinical benefit [15], it is the latter question that most directly drives the clinical decision-making, and so the process that generates the data we observe. Consequently, for this research, we will focus on whether the ATP III treatment thresholds are crossed, and leave to later research the question of examining raw changes in LDL levels.

The decision regarding whether to adopt treatment can thus be rationalized as the outcome of a utility maximization problem, where patients receive utility from health and some numeraire good. Health is generated as a result of a production process where a pharmaceutical treatment is the primary productive input. While the literature on stain therapy is somewhat divided, we will not differentiate in this paper between the various statin (or indeed, other lipid-lowering drug classes). Thus, the demand for treatment is derived from the demand for health, and depends upon the patient's individual characteristics, the physician's practice style, and the information set that the patient possesses.

Conceptually, we posit that DTC can have two informational effects. First, it informs patients about the nature of the treatment, which helps the patient in choosing whether to seek a prescription (through a physician visit) and in matching the best product to their particular clinical need. Second, DTC can raise the patient's expectation of clinical effect thereby increasing the patient's commitment to the therapy. The latter effect would tend to encourage patients to adhere to therapy longer than they might be willing to adhere in the absence of DTC. Improved adherence should also translate into a greater probability that the LDL goals are met. The former effect would tend to improve the matching, which would also have a salutary effect on the likelihood of LDL goal attainment. Thus, in this paper, we will test the joint hypotheses that DTC for

statins affects both the adherence of patients to their prescriptions, and whether the patient gets their LDL levels below their individual ATP III thresholds.

Consequently, we will use the econometric methodology of bivariate probit. We model the joint probability that the patient adheres to some lipid-lowering pharmaceutical regime for at least 180 days ($Y_1 = 1$) and the probability that their measured LDL blood levels are below the thresholds defined by ATP III given their clinical comorbidities ($Y_2 = 1$). The probability of both events occurring becomes

Equation 1

$$\Phi(Y_1 = 1, Y_2 = 1) = \int_{-\infty}^{X\beta_1} \int_{-\infty}^{X\beta_2} f_\rho(t,s)\partial t \partial s$$

where

$$f_\rho(t,s) = [(1/(2\pi*(1-\rho^2)^{0.5})]\exp((-0.5)*(t^2-2\rho ts+s^2)/\ (1-\rho^2)^{0.5}).$$

The derivative of this function with respect to X can be shown to be

Equation 2

$$d\Phi / dX = F((X\beta_2 - \rho X\beta_1)/(1-\rho^2)^{0.5}) f(X\beta_1)\beta_1 + F((X\beta_1 - \rho X\beta_2)/(1-\rho^2)^{0.5}) f(X\beta_2)\beta_2$$

where $F(\ .\ )$ is the cumulative normal distribution function and $f(\ .\ )$ is the probability normal distribution function. Thus, the marginal effect of DTC (or any other variable) will depend upon the state of the world being predicted and the parameters estimated for all other covariates.

3.2. Data

We utilize a unique data set consisting of over 600,000 patients (including 3.6 million patient contacts, 3.8 million prescription records, 10.1 million vital signs, 12 million laboratory records, and 1.3 million preventive services records) extracted from the electronic medical records of approximately 90 primary care practices in 33 different states across the U.S.. We extract a sub-set of this data on patients who had ever been

diagnosed with hypercholesterolemia, who physician had visits in the years 1998-2004, and who had begun treatment with any statin (including, but not limited to, the three statins for which advertising data is available). These patient-level clinical observations were merged with monthly television advertising measures (dollars spent) for both national and local media market advertising for three brands of statin drugs (Lipitor, Pravachol, and Zocor) which represented the bulk of ad spending on statin drugs during this time period.

Data were obtained from the Practice Partner Research Network (PPRNet), which is headquartered at the Medical University of South Carolina (MUSC). PPRNet is a practice-based learning and research organization among ambulatory primary care practices across the United States (US) that use a common electronic medical record (Practice Partner™ by Physician Micro Systems, Inc. Seattle WA). Practices pool longitudinal data on diagnoses, laboratory studies, medications, vital signs, and other information quarterly for research and quality improvement activities. Currently, PPRNet has access to all medical record extracts of 91 community-based primary care practices in 32 states. We extracted data on all patients who had a diagnosis for hypercholesterolemia from practices active from 1998 through 2004. Eighty-eight practices are represented in this time frame.

3.3. Dependent Variables

The first of our two dependent variables is an indicator variable for whether the patient maintains therapy for at least 180 days. (Recall that all patients in the data have begun lipid-lowering therapy.) Our data contains many details on all prescriptions written for each practice's patients. These include drug name, strength, number of pills to take each day, number of pills supplied, and number of refills permitted. Thus, we can calculate the number of daily doses available for each prescription written (including refills) which is the initial length of treatment. We then add to that initial length any additional daily doses that arise from renewals of the prescription in the

future. The sum of all daily doses across initial prescription, refills and renewals becomes our measure of spell length.

In calculating our dependent variables, two additional factors must be weighed. First, there are multiple pharmaceutical agents that are available for lipid reduction. Since we are examining the hypothesis that DTC for statins affects lipid-lowering therapy adherence and effect, we include prescriptions for any lipid-lowering agent in our spells (i.e., we do not pay attention to therapy switching – an issue that is left for future research). Second, while daily adherence to therapy is clearly the ideal, patients often forget to take their medications. Such temporary lapses would not be considered discontinuing therapy among clinicians. Consequently, before we consider a spell to have ended, we require that the patient run out of daily doses for at least 90 days. Once we have constructed the treatment spells for each patient, we then create our first dependent variable, which equals 1 if the spell lasts at least 6 months, and 0 otherwise. Approximately 65 percent of the patients who initiate therapy adhere for at least 180 days.

Our second dependent variable is whether or not patients reached their LDL goals. Evidence-based LDL cholesterol goals are defined in the NIH (2001) Table 1XX summarizes our adaptation of the ATP III guidelines to determine LDL goal. We then extracted the LDL cholesterol lab results for each person that was closest to the date six months after their first prescription with a statin. Patients were defined as being at goal if their follow-up LDL level was at or below those levels listed in Table 1XX for that patient. (Note that we were able to follow the ATP III criteria for all clinical comorbidities with the exception of smoking status and family history of premature cardiovascular disease, since these two factors are not available in our data. We proxy for smoking status using diagnoses of chronic obstructive pulmonary disease (COPD), since this strongly suggests a patient was a smoker, though of course, many people in the sample are smokers who have not developed COPD, so that the proxy is imperfect.)

Table 1: Defining LDL Goals

LDL Goal (mg/dL)	Risk Factors	
	Hypertension, HDL < 40 mg/dL, Age > 44 (men) or 54 (women) Diagnosed with COPD (smoking proxy)	***Diagnosed CVD***
<160	Zero or one	No
<130	Two or three	No
<100	Not applicable	Yes

Source: Adapted to observable data from National Heart Lung and Blood Institute. National Institutes of Health. *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)* .

Table 3 presents means of LDL goals and goal attainment for patients in the entire sample, and those patients who began therapy during a high overall DTC month (defined as being a month in the 75th percentile or higher of total DTC spending) and a low overall DTC month (defined as being in the 25th percentile of lower of total DTC spending). Approximately 17 percent of the sample had an LDL goal of 100 mg/DL, 40 percent had a goal of 130 mg/DL, and 43 percent had a goal of 160 mg/DL.

As may be expected, patients whose goals were higher (i.e., easier to attain) were more likely to achieve those goals, as seen in the third column of the table. We also found preliminary evidence that DTC had an effect on goal attainment. For each of the three LDL blood goal levels, patients who began therapy during a high DTC month (column 3) had a higher rate of goal attainment than patients who initiated therapy during a particularly low DTC month (column 4). This difference was clearly the greatest for patients who had the most restrictive LDL goal.

Table 2:
Percent of Population at LDL Target
Overall, and by advertising market level

Target LDL (mg/DL)	Number (%)	Overall Number at Target (%)	High DCA Exposure Number at Target (%)	Low DCA Exposure Number at Target (%)
<100	18,929 37.0%	10,795 57.0%	2,785 58.6%	2,000 52.9%
<130	13,681 26.8%	11,034 80.7%	2,742 81.4%	2,029 78.9%
<160	18,490 36.2%	16,944 91.6%	4,199 92.1%	3,156 91.9%
All	51,100 100.0%	38,773 82.0%	9,726 76.7%	7,185 73.4%

However, these unadjusted rates did not take the details of patient characteristics or general practice tendencies (and patient mix) into account. Everything else being equal, one would expect that any impact of DTC would be largest among those patients with the LDL goals that are least difficult to achieve (160 mg/DL). Thus, while the raw rates suggested the counter-intuitive result that DTC effects were larger for patients with the most stringent LDL goals, a multivariate analysis was needed to assure that this correlation was not confounded.

3.4. Explanatory Variables

We obtained national and local advertising information from Competitive Media Reporting, Inc. (CMR), which collects data on media advertising for all products, including pharmaceuticals, at the market (e.g., city) level. The data is specific to the brand name of the product and contains information on which products were advertised and how many dollars were spent on advertising on both national and local television each month. We used 1000s of dollars in ad spending by month summed across the three drug brands as our measure of DTC advertising (thus, we are estimating only drug-class level effects, and are not attempting to identify the impact of DTC for the individual brands separately). Patients and physician practices were assigned to the nearest local media market (by mileage to the MSA center). We eliminated practices which were more than 100 miles from the geographic center of the nearest media market. DTC advertising was measured at the time (month) that each patient began their individual spell of treatment with a statin drug.

Following Donohue, et al. [10] we create a dichotomous measure of DTC intensity. We created an indicator variable which equaled one if the beginning of the patient's statin use occurred during a month when DTC was in the upper 25th percentile of expenditures. For local advertising this corresponded to monthly spending of $7,900 or higher per market and month on all three statins for which data are available. For national advertising, this corresponded to a monthly spending of $7,494,900 or higher. Again, note that while we only measure DTC for Lipitor, Pravachol and Zocor, we examine all patients who were treated with any statin therapy for their elevated cholesterol.

We extracted all relevant clinical information from the PPRNet data. The independent variables used in both sides of the bivariate probit are: patients' baseline LDL levels, age (in years) and indicator variables for whether the patient is female, has diagnoses for coronary disease, diabetes, hypertension and COPD. We also include

physician practice fixed effects and year indicators. Table 3 lists the relevant characteristics of our sample.

Table 3 - Sample Characteristics

CHARACTERISTIC	Number	(%)
Remain on therapy for at least 180 days	33,047	(65%)
12 Month LDL Goal Attainment		
At goal	41663	(82%)
Not at goal	9078	(18%)
DCA Television Advertising		
Statin use initiated in heavy local advertsing month and metropolitan area	13952	(27%)
Statin use initiated in heavy national advertsing month	13855	(27%)
Gender		
Female	25319	(50%)
Age (Average)	60.6	
Clinical comorbidities		
Initial average LDL level (mg/DL)	133.8	
Coronary disease	7474	(15%)
COPD	2003	(4%)
Hypertension	26448	(52%)
Diabetes	13145	(26%)
Year Statin Therapy Began		
1998	2084	(4%)
1999	2329	(5%)
2000	3202	(6%)
2001	6961	(14%)
2002	11326	(22%)
2003	13803	(27%)
2004	11036	(22%)
Total Sample Size	51,100	

4. RESULTS

One concern that we addressed prior to estimating the models was how to represent the effect of time in the process of achieving LDL blood level goals. Certainly, the medical profession has paid increasing attention to the need to control LDL levels, as evidence has mounted about the risks associated with elevated blood LDL cholesterol.

In addition, clinical trials have found evidence that statin use is associated with a range of protective effects, such that clinicians have become increasingly careful to encourage patients to adopt daily statin therapy. These stylized facts raise two questions.

First, we needed to determine whether we were observing a different type of patient population for elevated LDL with statins as time progressed. The statistical problem that this raises is that if, over time, clinicians are increasingly persuading patients with relatively borderline LDL levels to begin using statins, then the likelihood of a successful outcome (blood LDL levels below the ATP III guidelines) could have risen due simply to the fact that the average patient has less far to go to reach his or her goals. If DTC also generally trended up, then this selection effect would lead to spurious correlation. Figure 1 graphs the average LDL blood level prior to initiation of statin therapy from our sample over time. (Recall that all patients in the sample have begun therapy.) There was some apparent downward trend in starting LDL levels, which suggested that selection effects may play a role in the process. We controlled for this by including starting blood LDL levels as a regressor. (Some observations are missing pre-treatment LDL levels since practices did not retroactively enter data from the paper charts when they adopted the electronic medical records. We imputed missing LDL levels using a multivariate regression and also included an indicator variable in the estimated models that equaled 1 when pre-treatment LDL was imputed, and equaled 0 otherwise. The parameter estimates for this nuisance indicator variable are not shown in the tables.)

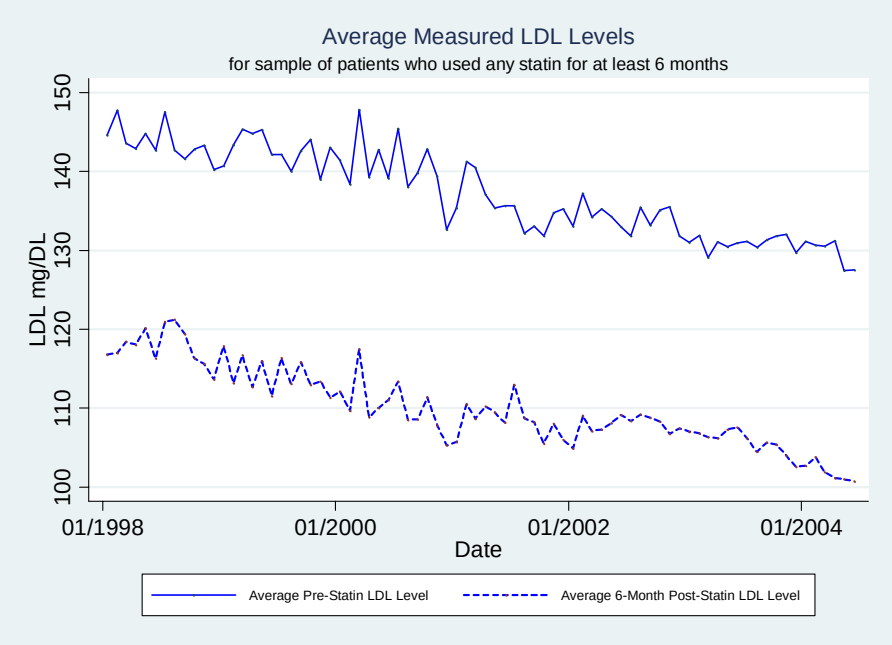

Figure 1 also sheds light on the second question that was raised regarding the effect of time in our models. The lower line in Figure 1 graphs the average LDL level measured post-treatment. Again, these measurements were the lab measurements closest in time to 6 months after initiation of statin treatment. A downward trend in post-treatment LDL levels was apparent. The implications were clearer in Figure 2, which graphs the percentage of patients who were at goal 6 months after initiating statin therapy, as well as the average total (summed local and national) DTC spending. Clearly, rates of "success" were rising over the entire range of the data. In addition, the trend appears to have been relatively linear. Consequently, we needed to control for time in the bivariate probit models. We did so by including "0/1" indicator variables for the year that statin therapy began (with 2004 being the excluded categorical variable).

Finally, we needed to accommodate the fact that DTC may have affected patients differently. Healthier patients – with the less restrictive LDL goals of 160 mg/DL and 130 mg/DL – may have been more responsive to health messages of all types, including DTC. If so, the impact of DTC on matching therapy or adherence would have differed across patients with different LDL goals. We test for this by running estimations for the

three different types of LDL goals, after our initial estimates reject pooling using a likelihood ratio test.

Table 4 outlines the basic results of our estimations. The top part of the table shows the impact of advertising on adherence, across the three different types of patients. In the model without fixed effects, local advertising is statistically significant with a positive impact in each model (though one coefficient has a z-statistic of 1.939, slightly below the 5 percent cut-off threshold). The coefficients are very similar in magnitude across the three models. For the fixed effect models, again all three models show a positive impact of high adverting on adherence. In these scenarios, the coefficients are again of the same magnitude, and the z-statistics are much higher than in the model without fixed effects.

With respect to national advertising, in the models without fixed effects, two of the three models show a statistically significant positive impact of advertising on adherence. (The third model has a coefficient z-statistics of 1.89.) The models with fixed effects each show a statistically significant impact of advertising on adherence.

Thus, the results of the first part of the table reveal that DTC, both local and national, has an important impact on adherence. All of the fixed effects models have statistically significant impacts. Four of the six coefficients in the models without fixed effects are statistically significant, while the other two coefficients are close to being significant.

Table 4
Coefficients on National and Local Advertising
Across LDL Goals
(t-statistics in parentheses)

	Without Fixed Effects			*With Fixed Effects*		
	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160
Adherence						
Local Advertising	0.243 (2.00)	0.254 (2.01)	0.246 (1.94)	0.207 (6.01)	0.218 (6.07)	0.167 (3.93)
National Advertising	0.093 (3.26)	0.029 (1.89)	0.123 (3.98)	0.101 (3.93)	0.079 (2.81)	0.142 (4.48)
Attain LDL Goal						
Local Advertising	0.0097 (0.27)	0.103 (2.72)	0.039 (0.97)	0.0085 (0.26)	0.081 (2.74)	0.00047 (0.01)
National Advertising	0.063 (2.69)	0.053 (1.91)	0.026 (0.81)	0.063 (2.68)	0.052 (1.86)	0.029 (0.66)
# of Obs./ % adherence/ % reaching goal	18,929/ 65.75%/ 57.03%	13,681/ 65.97%/ 80.65%	18,490/ 65.19%/ 91.64%	18,929/ 65.75%/ 57.03%	13,681/ 65.97%/ 80.65%	18,490/ 65.19%/ 91.64%

Also included as regressors, but not shown: patient pre-treatment LDL level, age, gender, diagnosis of hypertension, year indicators, and (where appropriate) physician practice fixed effects.

The lower part of Table 4 summarizes the impact of DTC on patients attaining their LDL goals. Local advertising statistically increases the probability that patients with an LDL goal of 130 reach their goal in models without and with fixed effects. The impacts of local advertising on other types of patients are not significant. National advertising is shown to statically impact the probability that patients with LDL goals of 100 attain their goals in models with and without fixed effects. The other models do not show statistically significant impacts of national advertising on goal attainment, though the coefficients on patients with LDL goals of 130 are marginally significant. It is not surprising that patients with LDL goals of 160 mg/DL are not responsive to national or local DTC. While that group of patients have as much room for improvement as the other two groups with respect to adherence (having an average rate of 6-month adherence of around 65%), note that the average rate of goal attainment is nearly 92% - which limits the magnitude of any possible improvement. Thus, the relatively liberal ATP III LDL treatment threshold creates a clear ceiling effect.

With respect to the other explanatory variables in the adherence equation, higher LDL levels were associated with a higher probability of adherence in four of the six models. Age had a negative impact on adherence in two of the models. The presence of a coronary condition or hypertension had a positive impact on adherence in one model each. In the attainment equation, initial LDL levels, age and being female were significant in each model, with older patients more likely to attain their LDL goals, and female patients and patients with higher initial LDL levels less likely to attain their goals. (Full results are available from the authors.)

As discussed above, the parameter presented in Table 4 do not convey the magnitude of the effect of DTC (or any other variable) on the joint likelihood that patient adhere to therapy and cross the ATP III LDL treatment thresholds. As shown in Equation 2, the actual marginal effect on this joint probability for any variable depends on the full vector of estimated parameters as well as the points in the variable space used for evaluation. One can calculate the marginal effect on the probability of four joint outcomes (adhere/attain, do not adhere/attain, adhere/do not attain, and do not adhere/ do not attain). We are interested in the marginal impact that exposure to high advertising has on the joint probability that a patient is both adherent and has reached their LDL goal. Table 5 presents those estimates and the associated joint t-tests (each evaluated at the means of the sample variables).

Table 5
Marginal Effects
On Joint Probability of Adherence and Reaching Goal
(t-statistics in parentheses)

	Without Fixed Effects			**With Fixed Effects**		
	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160
Local Advertising	0.051 (1.86)	0.090 (2.38)	0.087 (1.95)	0.043 (4.00)	0.076 (6.75)	0.057 (3.69)
National Advertising	0.036 (4.17)	0.025 (2.46)	0.044 (4.43)	0.037 (4.85)	0.031 (3.32)	0.050 (4.81)

In the models without fixed effects, high regimes of local advertising increase the joint probability of patients attaining both adherence and LDL goals between 5 and 9 percent. Only one of the three coefficients is statistically significant, however, though the other two are marginally significant. In the fixed effects model, all three coefficients are statistically significantly, with high local advertising regimes increasing the joint probably of adherence and goal attainment between 4 and 8 percent. All of the models show that high regimes of national advertising increase the joint probability of adherence and goal attainment, with effects ranging from 3 to 5 percent.

5. CONCLUSIONS

Coronary Heart Disease (CHD) is the leading cause of mortality in the United States. Over 12 million people in the U.S. have some history of CHD. High cholesterol has been identified as a primary risk factor in CHD, and control of blood cholesterol (lipid) levels has been identified as one of the most important pathways to delay the onset of active CHD in patients in the U.S. Further, while this condition is amenable to treatment using pharmaceutical therapies, clinicians continue to struggle with improving the rate of adequate lipid control. Nearly 35 million people in the U.S. have cholesterol levels that are considered clinically high, and therefore increasing the risk of CHD [13]. Statins have been demonstrated to be highly effective at not only reducing levels of cholesterol in the blood to clinically acceptable baselines but also at reducing mortality from CHD. Statin benefits have been measured in the range of a 34 percent reduction in relative risk for coronary events to a 42 percent relative risk reduction in coronary mortality [14]. Despite the clear need for and benefits of stain therapy, clinicians struggle to increase the rate of use among their patients.

Thus, to the extent that DTC for branded statin drugs might prompt regular use of lipid lowering pharmaceuticals, it could be seen as a useful tool toward improving patient lipid levels. On the other hand, if all DTC for branded statins accomplishes is switching patients between advertised products, then one would expect little or no significant improvements in overall adherence or in lipid control. This study

investigates this issue – and asks whether a higher level of DTC does improve adherence and goal attainment, and if so, what is the magnitude of this effect.

The results here strongly indicate that DTC advertising for statins has important health impacts for patients. Local and national advertising have been shown to increase the prescription adherence for all patients. Perhaps more importantly, both national and local advertising have been shown to increase the probability that patients with LDL goals of 100 (the patients most at risk) attain their LDL goals. Overall, exposure to high levels of DTC prior to adopting statin therapy raises the joint probability that patients both adhere to their therapeutic regimes and attain their LDL goals from between 3 to 5 percent.

Direct to consumer advertising remains a controversial issue. The results here, however, indicate that such advertising can have beneficial results for patients with high cholesterol levels. Advertising has the potential to increase levels of adherence and LDL goal attainment. Given this, we advise caution before additional restraints are placed on such advertisements.

6. REFERENCES

1. Masson, A and Rubin, P. Matching prescription drugs and consumers: The benefits of direct advertising. *New England Journal of Medicine.* 1985; 313: 513-15.

2. Rubin, P. Economics of prescription drug advertising. *Journal of Research in Pharmaceutical Economics.* 1991; 3: 29-39.

3. Keith, A. Regulating information about aspirin and the prevention of heart attack. *American Economic Review.* 1995; 85: 96-99.

4. Weissman, J, et al. Consumer reports on the health effects of direct to consumer advertising. *Health Affairs Web Exclusive.* 2003; 22: 1-5.

5. Brekke, K and Kuhn, M. Direct to consumer advertising in pharmaceutical markets. *Journal of Health Economics.* 2006; 25: 102-130.

6. Calfee, J, Winston, C, and Stempski, R, *Direct-to-consumer advertising and the demand for cholesterol reducing drugs*. 2002, AEI.

7. Zachry, W, et al. Relationship between direct-to-consumer advertising and physician diagnosing and prescribing. *American Journal of Health System Pharmacy.* 2002; 59: 42-49.

8. Iizuka, T and Zin, G, *The effects of direct-to-consumer advertising in the prescription drug markets*, A.E.A.A. Conference, Editor. 2003: Philadelphia.

9. Wosinska, M. Direct-to-consumer advertising and drug therapy compliance. *Journal of Marketing Research.* 2005; 42: 323-332.

10. Donohue, J, et al. Effects of pharmaceutical promotion on adherence to the treatment guidelines for depression. *Medical Care.* 2004; 42: 1176-1185.

11. Bradford, WD, et al., *The effect of direct to consumer television advertising on physician prescribing behavior for the treatment of osteoarthritis*, in *Health Affairs*. 2006, forthcoming.

12. Bradford, WD, et al. The effect of direct to consumer television advertising on the timing of treatment. *AEI-Brookings Papers.* 2005; 05-19: 1.

13. American Heart Association, A, *Cholesterol Statistics*. 2006, American Heart Association.

14. Grundy, S, et al. Hepatic lipase activity influences high density lipoprotein subclass distribution in normotriglyceridemic men. Genetic and pharmacological evidence. *Journal of Lipid Research.* 1999; 40: 229-34.

15. National Institutes of Health, NHLBI, *Third report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii).* 2001: Washington DC.